DECLARATION

I, Mari YUGE, a national of Japan, c/o Asamura Patent Office, p.c. of 331-340, New Ohtemachi Building, 2-1, Ohtemachi 2-chome, Chiyoda-ku, Tokyo, Japan, do hereby solemnly and sincerely declare:

1) THAT I am well acquainted with the Japanese language and English language, and

2) THAT the attached is a full, true, accurate and faithful translation into the English language made by me of Japanese Patent Application No. 2003-273176.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001, of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 15th day of February, 2011.

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[Kind of Document] Claim

[Claim 1]

A release-sustaining starch powder having a water retention capacity of 700% or more, a collapse time of 3 hr or more and a gel indentation load of 400 g or more.

[Claim 2]

A composition comprising release-sustaining starch powder according to claim 1 and one or more active ingredients.

[Claim 3]

A method for producing starch powder according to claim 1, characterized by heating a starch raw material in the presence of water to form a starch emulsion containing particles with a shell thin-film structure and having a content of swollen or dissolved amylose and amylopectin in the range of 20 to 90%, and drying the emulsion.

[Kind of Document] Description

[Title of the Invention] RELEASE-SUSTAINING STARCH POWDER

[Technical Field]

[0001]

The present invention relates to a composition comprising starch powder and one or more active ingredients, and a method for producing the starch powder. More particularly, it relates to starch powder as a release-sustaining base ingredient for controlling the concentration of an active ingredient(s) in medicines, agrochemicals, fertilizers, feed, food, industry, cosmetics, etc.

[Background Art]

[0002]

As examples of composition having sustained-release properties, there are solid sustained-release medicines for medical use. The solid sustained-release medicines are very useful for, for example, the following reasons: since they control the blood level of the active ingredient(s), they reduce the frequency at which the medicine must be taken, to improve the ease of taking; they can improve the persistence of active ingredients that have a short half-life in a living body; and they can reduce the side effects of the active ingredients that have a narrow range between a minimum

effective blood concentration and a side effect exhibition concentration. Regarding conventional solid sustained-release medicines, there are matrix type medicines obtained as sustained-release tablets by the use of a hydrophilic polymer capable of forming a gel upon contact with water, and reservoir type medicines obtained as sustained-release granules by coating core particles with an active ingredient(s) and then coating the surface of the coated particle with a coating film capable of imparting sustained-release properties. Tablets are preferable to capsules and granules from the viewpoint of ease of taking, but reservoir type sustained-release tablets have been disadvantageous in that when the sustained-release granules are compressed into the tablets, the coating film capable of imparting sustained-release properties is destroyed, so that the controlled release of the active ingredient(s) by dissolving becomes difficult.

[0003]

On the other hand, hydrophilic polymers such as methyl cellulose (MC), hydroxypropyl cellulose (HPC) and hydroxypropylmethyl cellulose (HPMC) are used as a release-sustaining base ingredient used in the matrix type sustained-release preparations. These hydrophilic polymers are advantageous, for example, in that they impart sustained-release properties by the formation of a complete gel layer by hydration in a solution having a low ionic strength, are hardly affected by pH, and are

excellent in the stability of release by dissolution over a long period of time. They, however, have the following problem, which is called dose dumping: since it becomes impossible to hydrate the polymer in a solution having an intermediate or higher ionic strength, their gelation is suppressed, so that a large portion of the active ingredient(s) of a pharmaceutical preparation designed to have sustained-release properties is rapidly released, thus, the preparation exhibits no sustained-release properties. When the dose dumping occurs, the resulting rapid increase of the active ingredient(s) in the blood can induce death, depending on the efficacy of the active ingredient(s) that have a narrow range between the minimum blood level and the concentration where side effects are exhibited. Since the value of ionic strength in the gastrointestinal tract varies depending on regions of the tract and the food consumed, there has been a desire for a release-sustaining base ingredient which makes it possible to avoid the dose dumping in a wide ionic strength value range throughout the gastrointestinal tract.

[0004]

Patent document 1 describes simultaneous use of pregelatinized starch and a hydrophilic polymer such as hydroxypropyl cellulose or hydroxypropylmethyl cellulose as a means far avoiding the dose dumping. However, the pregelatinized starch (preferably drum-

dried waxy corn starch) used in this reference has no sustained-release effect in itself and is such that sustained-release properties are imparted by a release-sustaining base ingredient other than the pregelatinized starch. In addition, the pregelatinized starch is disadvantageous in that since the pregelatinized starch has only auxiliary effect on the release-sustaining base ingredient, both the base ingredient and this auxiliary are necessary and the amounts added should be large, resulting in an increased size of a preparation.

[0005]

As starch used in the fields of medicines, agrochemicals, fertilizers, feed, food, industry, cosmetics, etc., there are pregelatinized starch, partly pregelatinized starch, crosslinked starch and the like. They are used as a disintegrating agent mainly in the medicine field.

[0006]

All of the starches described in patent documents 2 to 11 rapidly collapse and do not impart any sustained-release properties. They are essentially different in the following respects from the starch of the invention, from which tablets that contain 60 to 100% of the starch powder are not disintegrated in 3 hours or more. That is, the modified starch of patent document 2 has a low degree of swelling of 2.5 to 12 and breaks down in 30 minutes. The waxy starch of patent document 3 is such that tablets containing 50% of the

waxy starch are disintegrated within 60 seconds. The β-starch with an α-starch surface of patent document 4 is such that tablets containing 17 to 30% of the β-starch are disintegrated within 2 minutes. The β-starch having 1 to 4% of α-starch adhered thereto of patent document 5 is such that tablets containing 17 to 87% of this β-starch are disintegrated within 20 seconds. The starch of patent document 6, which is obtained by 5 to 20% pregelatinization of the surface of β-starch, breaks down within 2 minutes. The modified starch of patent document 7 has a cold-water-soluble matter content of 10 to 20%, and tablets containing 64 to 80% of this modified starch are disintegrated within 20 minutes. The processed starch of patent document 8 has a low degree of swelling of 3.0 to 6.0 and the tablets containing 10% of this processed starch are disintegrated within 6 minutes. The processed starch of patent document 9 has a low cold water-soluble matter content of less than 10% by weight, a small swelling volume of 3 to 15 ml/g and a low water retention capacity of at most 610% and breaks down within 2 minutes. Patent document 10 is crosslinked starch powder having a low swelling property (swelling property in cold water: 3 to 25 ml) and breaks down more rapidly than Starch 1500 (Comparative Example 6 in the invention). The processed starch of patent document 11 has a small swelling volume of 3 to 15 ml and is the starch represented by PCS (Comparative Example 5 in the

invention) and Starch 1500 (Comparative Example 6 in the invention). Thus, these starches are essentially different from the starch of the invention.

[0007]

On the other hand, pregelatinized starch used mainly in the food field as a thickening agent, feed for eel breeding or the like has been disadvantageous in that a gel formed by the starch is destroyed in the presence of α-amylase, resulting in a deteriorated release-sustaining capability, as reported in Chem. Pharm. Bull., 35(10)4346-4350(1987). It has been disadvantageous also in that at a high ionic strength, it loses release-sustaining properties.

[0008]

Patent document 1: Japanese Patent Application Kohyo No. 2002-541090

Patent document 2: JP-B-46-21471

Patent document 3: JP-A-48-68726

Patent document 4: JP-B-53-3275

Patent document 5: JP-B-62-7201

Patent document 6: JP-B-58-27774

Patent document 7: JP-B-56-11689

Patent document 8: JP-A-58-32828

Patent document 9: JP-B-59-47600

Patent document 10: JP-B-63-7531

Patent document 11: JP-A-6-100602

[Disclosure of Invention]

[Problem to be solved by the Invention]

[0009]

The invention is directed to provide a novel starch-based release-sustaining base ingredient which is as follows: the base ingredient is starch powder as a release-sustaining base ingredient for controlling the concentration of an active ingredient(s) in medicines, agrochemicals, fertilizers, feed, food, industry, cosmetics, etc.; it is a release-sustaining base ingredient which has a sufficient release-sustaining capability to constitute a sustained-release preparation mainly for medicinal use, assures pH stability and long-term stability, and is convenient; and since it is not affected by ionic strength, it is free from the dose dumping problem, so that it permits accurate control of an active ingredient(s), for example, throughout gastrointestinal tract.

[Means for Solving the Problem]

[0010]

The inventors earnestly investigated the water retention properties, disintegration properties and gel characteristics of starch powder, and consequently found a starch powder which has all of sufficient release-sustaining capability, pH stability and long-term stability and does not cause the dose dumping because it is not affected by ionic strength, thereby the invention has been accomplished. That is, the invention is as follows.

[0011]

(1) A release-sustaining starch powder having a water retention capacity of 700% or more, a collapse time of 3 hr or more and a gel indentation load of 400 g or more.

(2) A composition comprising release-sustaining starch powder according to the above item (1) and one or more active ingredients.

(3) A method for producing starch powder according to the above item (1), which comprises heating a starch raw material in the presence of water to form a starch emulsion containing particles with a shell thin-film structure and having a content of swollen or dissolved amylose and amylopectin in the range of 20 to 90%, and drying the emulsion.

[0012]

The invention is a novel starch powder which has satisfactory release-sustaining properties owing to its high α-amylase resistance that is not possessed by conventional natural or processed starch, and which is excellent in pH stability and long-term stability and, moreover, is not affected by ionic strength, so that it is free from the dose dumping problem associated with conventional release-sustaining base ingredients and hence permits accurate control of an active ingredient(s).

[Best Mode for Carrying Out the Invention]

[0013]

The invention is explained below in detail.

The starch powder of the invention should have a water retention capacity of 700% or more. The term "water retention capacity" is defined as the volume of pure water retained by starch after the centrifugation (2000G, 10 minutes) of a dispersion of 1 g of dry starch powder in pure water. When the water retention capacity is less than 700%, the starch powder is hydrated to form no gel, resulting in disintegration of tablets, or the starch powder cannot exhibit satisfactory release-sustaining properties because of rapid diffusion of an active ingredient(s) even when the starch powder forms a gel layer. The gel-forming capability is enhanced with an increase of the water retention capacity. When the water retention capacity is high, the gel is desirably not destroyed even at a high ionic strength, though the maximum water retention capacity is dependent on characteristics of a starch raw material and is at most 3000%. The water retention capacity is 1000% to 3000%.

[0014]

In addition, the starch powder of the invention should have a collapse time of 3 hours or more. The term "collapse time" is defined as the disintegration time, in a test solution, of a cylindrical molded article with a diameter of 0.8 cm obtained by compressing 0.2 g of starch powder at 50 MPa. The test solution is the second solution (pH 6.8) prescribed in the Japanese Pharmacopoeia, the 14th

revision, p. 204 and a disintegration test is carried out by the use of an auxiliary plate according to the disintegration test method described in the Japanese Pharmacopoeia (14th revision). When the collapse time is less than 3 hours, no satisfactory release-sustaining properties can be attained. The upper limit of the collapse time depends on the desired degree of release-sustaining properties and is at most 240 hours.

[0015]

Furthermore, the starch powder of the invention should have a gel indentation load of 400 g or more. The term "gel indentation load" is defined as a maximum load applied when a cylindrical adapter is pressed for 3 mm at a rate of 0.1 mm/sec into a gel formed by immersing, in pure water for 4 hours, a cylindrical molded article with a diameter of 1.13 cm obtained by compressing 0.5 g of starch powder at 50 MPa. The term "maximum load" means the following: when a layer of the gel is broken, the term means a load value at the time of the breaking: and when the gel layer is not broken, the term means a maximum load value which the adapter applies before it intrudes for 5 mm into the gelatinized cylindrical molded article. When the gel indentation load is less than 400 g, the diffusion of an active ingredient(s) in a gel layer formed by the starch powder becomes rapid, so that no satisfactory release-sustaining properties are exhibited. Although the gel indentation load is

preferably high because the release-sustaining capability of the starch powder is enhanced with an increase of the gel indentation load, it is at most about 3000 g.

[0016]

A method for producing the starch powder of the invention is described below.

The starch powder of the invention is obtained by heating a starch raw material in the presence of water to form a starch emulsion containing particles with a shell thin-film structure and having a content of swollen or dissolved amylose and amylopectin in the range of 20 to 90%, and drying the emulsion. Although the following is an example and the method is not limited thereby, the starch powder is obtained by drying the emulsion after, if necessary, maintaining the emulsion at a temperature at which the emulsion shows a maximum viscosity in an amylogram or a temperature lower than and close to the aforesaid temperature. A preferable temperature is 60 to 150°C. The temperature is more preferably 90 to 140°C, particularly preferably 90 to 130°C.

[0017]

The starch raw material referred to herein is not particularly limited so long as it contains a starch material such as natural starch, aged starch or crosslinked starch of rice, glutinous rice, corn, waxy corn, amiro corn, sorghum, wheat, barley, taro, green

gram, potato, lily, dogtooth violet, tulip, canna, pea, shiwa pea, chestnut, arrowroot, yam, sweet potato, broad bean, snap bean, sago, tapioca (cassava), bracken, lotus, water caltrop or the like. Potato is preferred because its particles have a high swelling property, so that the water retention capacity can easily be controlled to be high. A material obtained by subjecting a starch raw material to wet heat treatment such as heat treatment at 100 to 130°C under reduced pressure as discussed in JP-A-4-130102 or JP-A-7-25902 is more preferred because when such a material is used, the gelatinizatian temperature is raised, so that the swelling properties of particles are enhanced. As the starch raw material, one or a mixture of two or more of the above-exemplified materials may be freely used. The size of particles of the starch raw material is preferably as large as possible from the viewpoint of ease of expanding.

[0018]

The shell thin-film structure referred to herein is inherent in the starch raw material and is clearly distinguished from a flaky, massive or the like structure formed, for example, by the conversion of swollen or dissolved amylose and amylopectin to β-amylose and β-amylopectin. Particles having the shell thin-film structure inherent in the starch raw material are improved in water retention with a rise of heating temperature because of swelling, and the particles

having an improved water retention are swollen in water to be increased in particle size. When the heating temperature is higher than a certain temperature intrinsic to the starch, the shell thin-film structure is destroyed. The reason is as follows: in starch particles, with a rise of the heating temperature, amylose is released by dissolution and amylose and amylopectin, which constitute the shell thin-film structure, are swollen, dispersed as molecules, and then gradually dissolved. Starch particles exhibit the highest water retention immediately before the destruction of the shell thin-film structure.

[0019]

When 1 g of the starch powder of the invention is dispersed in 100 cm^3 of pure water and stands for 16 hours, the lower layer portion of the dispersion separated into upper and lower layers is observed under an optical microscope (magnification: 10), the shell thin-film structure inherent in a starch raw material for the starch powder is completely present without loss thereof. On the other hand, in the case of pregelatinized starch, nothing is observed in the above-mentioned lower layer portion, or a flaky, massive or the like shell structure formed by the conversion of swollen or dissolved amylose and amylopectin to β-amylose and β-amylopectin is observed in the lower layer portion.

[0020]

For imparting release-sustaining properties, resistance to α-amylase and resistance to ionic strength, the amount of amylose and amylopectin, each of which is present in a swollen or dissolved state, should be in a definite range. The term "swollen or dissolved amylose and amylopectin" means amylose and amylopectin expanded or dissolved by heating of a starch raw material in the presence of water that are so transparent or semitransparent that their shapes cannot be observed under an optical microscope. Their amount can be determined by dispersing 1 g of starch powder in 100 cm^3 of pure water, allowing the resulting dispersion to stand for 16 hours and calculating the amount from the volume of the upper layer portion of the dispersion separated into upper and lower layers and the weight of solids in 30 cm^3 of the upper layer (the volume of the upper layer portion ÷ 30 x the weight of solids in 30 cm^3 of the upper layer ÷ the dry weight of 1 g of the starch x 100 (%)). The amount in the case of the starch powder of the invention ranges from 20 to 90%. When the amount is less than 20%, the water retention is insufficient, so that no release-sustaining properties are exhibited. This is not desirable. When the amount is more than 90%, the water retention is lowered, so that the resistance to α-amylase, release-sustaining capability and resistance to ionic strength are undesirably deteriorated.

[0021]

When the amount of swollen or dissolved amylose and amylopectin is controlled to be within the above range, the shell thin-film structures of starch particles are not completely lost and can be clearly observed in the lower layer portion in the above-mentioned measurement.

The volume of the lower layer portion of a dispersion separated into upper and lower layers, which is obtained by dispersing 1 g of starch powder in 100 cm^3 of pure water, followed by standing for 16 hours, is a value called "degree of swelling" and reflects the degree of pregelatinization of particles to a certain extent. This value is small when the pregelatinization is insufficient or too sufficient. The degree of swelling of the starch powder of the invention is approximately 3 cm^3 to 60 cm^3 and is preferably, in particular, 20 cm^3 to 50 cm^3.

[0022]

Pregelatinized starch and partly pregelatinized starch, which are used mainly in medicines, are obtained by gelatinizing natural starch by heating and then drying the gelatinized starch. As described in JP-B-59-47600, starch with excellent disintegrating properties can be obtained with starch mostly composed of particles with a shelf thin-film structure and inhibited as much as possible from releasing swollen amylose and amylopectin by dissolution by heating at a temperature which is above 50°C and below

a temperature about 10°C higher than an intrinsic gelatinization initiation temperature (which is a temperature lower than 90°C though depending on the kind of starch). Although such starch includes particles with a shell thin-film structure, sufficient water retention is impossible because of insufficient swelling in water, or the amount of swollen amylose and amylopectin is insufficient which results in an insufficient gel indentation load. Therefore, such starch does not exhibit release-sustaining properties.

[0023]

Pregelatinized starch used mainly in food is produced by a method such as drum drying at about 150°C or extrusion with an extruder at 120 to 160°C under high pressure. In pregelatinized starch obtained by such a method, its particles are excessively swollen because of too high a gelatinization temperature, almost no particles having a shell thin-film structure are present, and its particles have a flaky or massive shape different from a shell thin-film structure inherent in starch particles, which is formed by swollen or dissolved amylose and amylopectin and their conversion to β-amylose and β-amylopectin. Starch composed mainly of amylose and amylopectin swollen with loss of the shell thin-film structures by such excessive pregelatinization are not desirable because it has an insufficient water retention capacity, so that its resistance to α-amylase (release-sustaining capability)

and resistance to ionic strength are deteriorated.

[0024]

Although a method for the drying is not particularly limited, it includes, for example, freeze-drying, spray drying, drum drying, tray drying, air-drying, vacuum drying, and drying by solvent replacement. Industrially, spray drying and drum drying are preferred. The solid content of a liquid at the time of the drying is approximately 0.5% to 40%. When the solid content is less than 0.5%, the productivity is undesirably deteriorated. When the solid content is 40% or more, the viscosity becomes high, so that the yield is undesirably decreased.

[0025]

That is, the starch powder of the invention is as follows: starch particles are properly swollen or dissolved to adjust the amount of swollen or dissolved amylose and amylopectin to 20 to 90%, without completely destroying particles having a shell thin-film structure, thereby success has been achieved for the first time in the impartment of a high resistance to α-amylase, a high resistance to ionic strength and a sufficient release-sustaining capability, which are not possessed by conventional pregelatinized starch and partly pregelatinized starch.

[0026]

The composition including the starch powder referred to herein and one or more active ingredients

can be used for controlling the concentration of the active ingredient(s) in the fields of medicines, agrochemicals, fertilizers, feed, food, industry, cosmetics, etc. The amount of the starch powder of the invention incorporated into the composition of the invention is approximately 1 to 99.99%. When the amount is less than 1%, no effect of the starch powder of the invention can be obtained. When the amount is more than 99.99%, a sufficient amount of the active ingredient(s) cannot be added, so that the therapeutic effect, efficacy and the like of the active ingredient(s) cannot be expected. The starch powder of the invention is usually used in the range of 5 to 95%, preferably about 10 to about 90%.

[0027]

The active ingredient(s) referred to herein includes pharmaceutically active ingredients, agrochemical ingredients, ingredients for fertilizer, ingredients for feed, ingredients for food, ingredients for cosmetic, coloring maters, flavoring materials, metals, ceramics, catalysts, surfactants and the like. The active ingredient(s) may be in the form of any of powder, crystals, oil, a liquid, a semisolid and the like. The shape may be any of powder, fine granules, granules and the like. The active ingredient(s) may be coated to control the release by dissolution, to reduce bitterness, or the like. The active ingredients may be used alone or in combination.

[0028]

For example, for the pharmaceutically active ingredients, orally administrable drugs such as antipyretic analgesic antiphlogistics, hypnotic sedatives, sleepiness inhibitors, dinics, infant analgesics, stomachics, antacids, digestives, cardiotonics, drugs for arrhythmia, hypotensive drugs, vasodilators, diuretics, antiulcer drugs, drugs for controlling intestinal function, therapeutic drugs for osteoporosis, antitussive expectorants, antasthmatics, antibacterials, drugs for pollakiuria, tonics, vitamin preparations, and the like can be used. The active ingredients may freely be used alone or in combination.

[0029]

If necessary, the composition of the invention may contain other components such as disintegrating agents, binders, fluidizing agents, lubricants, correctives, flavoring materials, coloring matters, sweeteners, etc. besides the active ingredient(s) and the starch powder of the invention. The other components may be used as a diluent.

[0030]

The binders include, for example, sugars such as sucrose, glucose, lactose, fructose, trehalose, etc.; sugar alcohols such as mannitol, xylitol, maltitol, erythritol, sorbitol, etc; water-soluble polysaccharides such as gelatin, pullulan, carrageenan, locust bean gum, agar, konjak mannan, xanthan gum, tamarind gum, pectin,

sodium alginate, gum arabic, etc.; celluloses such as crystalline celluloses (e.g. "Avicel" PH-101, PH-101D, PH-101L, PH-102, PH-301, PH-301Z, PH-302, PH-F20, PH-M06, M15, M25, "Ceolus" KG-801 and KG-802, manufactured by Asahi Kasei Corp.), powdered cellulose, hydroxypropyl cellulose, methyl cellulose, etc.; starches such as pregelatinized starch, starch paste, etc.; synthetic polymers such as poly(vinylpyrrolidone)s, carboxyvinyl polymers, poly(vinyl alcohol)s, etc.; and inorganic compounds such as calcium hydrogenphosphate, calcium carbonate, synthetic hydrotalcite, magnesium aluminate silicate, etc. A binder selected from the above-exemplified binders may be used alone or two or more of them may be used in combination.

[0031]

The crystalline celluloses usable as the binder are preferably those having an excellent compactibility. Use of the crystalline cellulose having an excellent compactibility permits compression into tablets at a low striking pressure. Therefore, granule-containing tablets can be obtained which permit retention of the activity of an active ingredient(s) that is inactivated by striking pressure. Moreover, a hardness can be imparted by adding a small amount of such crystalline cellulose, and hence, a bulky active ingredient(s) or a drug containing various kinds of active ingredients can be made into tablets. Such crystalline cellulose is advantageous, for example, in

that in some cases, it permits reduction of the size of tablets, is excellent in ability to support a liquid component and can suppress hindrances in compression into tablets.

[0032]

The disintegrating agents include, for example, celluloses such as sodium croscarmellose, carmellose, calcium carmellose, sodium carmellose, low-substituted hydroxypropyl cellulose, etc.; starches such as sodium carboxymethyl starch, hydroxypropyl starch, rice starch, wheat starch, corn starch, potato starch, partly pregelatinized starch, etc.; celluloses such as crystalline cellulose, powdered cellulose, etc.; and synthetic polymers such as crospovidone, crospovidone copolymers, etc. A disintegrating agent selected from the above-exemplified disintegrating agents may be used alone or two or more of them may be used in combination.

[0033]

The fluidizing agents include silicon compounds such as hydrated silicon dioxide, light silicic anhydride, etc. These fluidizing agents may be used alone or in combination.

The lubricants include magnesium stearate, calcium stearate, stearic acid, sucrose fatty acid esters, talc, etc. A lubricant selected from the above-exemplified lubricants may be used alone or two or more of them may be used in combination.

[0034]

The correctives include glutamic acid, fumaric acid, succinic acid, citric acid, sodium citrate, tartaric acid, malic acid, ascorbic acid, sodium chloride, l-menthol, etc. A corrective selected from the above-exemplified correctives may be used alone or two or more of them may be used in combination.

The flavoring materials include orange, vanilla, strawberry, yogurt, menthol, oils (e.g. fennel oil, cinnamon oil, orange-peel oil and peppermint oil), green tea powder, etc. A flavoring material selected from the above-exemplified flavoring materials may be used alone or two or more of them may be used in combination.

[0035]

The coloring matters include food colors (e.g. food red No. 3, food yellow No. 5 and food blue No. 1), copper chlorophyllin sodium, titanium oxide, riboflavin, etc. A coloring matter selected from the above-exemplified coloring maters may be used alone or two or more of them may be used in combination.

The sweeteners include aspartame, saccharin, glycyrrhizic acid dipotassium salt, stevia, maltose, maltitol, thick malt syrup, powdered sweet hydrangea, etc. A sweetener selected from the above-exemplified sweeteners may be used alone or two or more of them may be used in combination.

[0036]

When the composition is used as a medicine,

the composition includes, for example, solid pharmaceutical preparations such as tablets, powders, fine granules, granules, extracts and pills. They can be produced by well-known methods such as extrusion granulation, crushing granulation, fluidized-layer granulation, high-speed stirring granulation, tumbling flow granulation and the like. The composition may be utilized not only as medicines but also as foods (e.g. confectionery, health food, texture improvers and dietary fiber supplements), solid foundations, bath agents, animal drugs, diagnostic drugs, agrochemicals, fertilizers, ceramic catalysts and the like.

[0037]

As an example of the composition, tablets are preferably prepared from the viewpoint of productivity, the ease of administration/ingestion and the ease of handling. The tablets are obtained by a direct tableting method, dry granule compression method, wet granule compression method, wet granule compression (extragranular addition of MCC) or the like. Although the tablets may be multi-core tablets containing, as inner cores, tablets previously obtained by compression molding, they are preferably, in particular, tablets obtained by direct tabletting, from the viewpoint of cost and ease.

The composition of the invention makes it possible to impart sustained-release properties to pharmaceutical preparations by a simple method including

mixing one or more active ingredients with the starch powder of the invention and formulating the mixture into tablets, a powder, granules, fine granules or the like using a known method. Therefore, troublesome operations such as coating of granules or tablets with a coating agent and the time and the labor required for the assurance of production conditions for a constant quality are unnecessary. Thus, the composition is useful also from the viewpoint of cost and productivity.

[0038]

Pharmaceutical preparations of the invention may have a coating for taste masking, dampproofing or the like. A coating agent includes, for example, cellulose type coating agents (e.g. ethyl cellulose, hydroxypropylmethyl cellulose phthalate, carboxymethylethyl cellulose, hydroxypropylmethyl cellulose acetate succinate, cellulose acetate succinate, cellulose acetate phthalate and cellulose acetate), acrylic polymer type coating agents (e.g. Eudragit RS, Eudragit L and Eudragit NE), shellac and silicone resins. These coating agents may be used alone or in combination. As a method for using these coating agents, a well-known method can be adopted. The coating agents may be dissolved in an organic solvent or suspended in water. A suspension of the coating agent in water may be granulated together with a pharmaceutically active ingredient(s) and other components.

[0039]

The pharmaceutical preparations of the invention include those which permit sustained release of an active ingredient(s) by diffusion from a gel layer formed substantially from starch. These pharmaceutical preparations can be prepared by well-known methods such as mixing, stirring, granulation, particle size regulation, tabletting, etc. The word "substantially" means that the starch powder of the invention is incorporated into the pharmaceutical preparation in order to endow the pharmaceutical preparation with the functions of the starch powder of the invention, such as a function of increasing the resistance to α-amylase, a function of enhancing the sustained-release capability and a function of assuring the sustained-release capability in a medium having a high ionic strength. The starch powder of the invention may be used alone or in combination with other release-sustaining base ingredients. For example, if formulation into a pharmaceutical form can be achieved by the addition of the starch powder of the invention in a case where a release-sustaining base ingredient such as HPMC, methyl cellulose, HPC or the like is co-used which does not bring about a sufficient sustained-release effect under a high ionic strength, the achievement can be considered to be attributable to the effect of the starch powder of the invention.

[0040]

The invention is illustrated in detail with the following examples, which should not be construed as limiting the scope of the invention. Methods for measuring physical properties in the examples and comparative examples are as follows.

(1) Water retention capacity (%)

W_0 (g) (about 1 g) of dried starch powder is placed in small portions in a 50-ml centrifuge tube containing about 15 ml of pure water and dispersed in the pure water while stirring until the dispersion becomes transparent or semitransparent. Pure water was added to fill the 50-ml centrifuge tube about 70% full therewith, followed by centrifugation (2000G, 10 minutes). After completion of the centrifugation, the separated upper layer is immediately discarded and then the water retention capacity is calculated from the weight W of the residue as the lower layer (the total weight of starch and pure water retained by the starch) by the following equation:

$$\text{Water retention capacity}(\%) = 100 \times [W - W_0] / W_0$$

[0041]

(2) Collapse time (hr)

The term "collapse time" is defined as the disintegration time, in a test solution, of a cylindrical molded article with a diameter of 0.8 cm obtained by compressing 0.2 g of starch powder at 50 MPa. The test solution is the second solution (pH 6.8) described in the Japanese Pharmacopoeia (14th revision,

p. 204) and a disintegration test is carried out by the use of an auxiliary plate according to the disintegration test method described in the Japanese Pharmacopoeia (14th revision).

(3) Gel indentation load (g)

The term "gel indentation load" is defined as a maximum load applied when a cylindrical adapter is pressed for 3 mm at a rate of 0.1 mm/sec into a gel obtained by immersing, for 4 hours in pure water, a cylindrical molded article with a diameter of 1.13 cm obtained by compressing 0.5 g of starch powder at 50 MPa. The term "maximum load" means the following: when a gel layer is broken, the term means a maximum load value at the time of the breaking; and when the gel layer is not broken, the term means a maximum load value, which the adapter applies before it intrudes for 5 mm into the gelled cylindrical molded article.

[0042]

(4) Amount (%) of swollen or dissolved amylose and amylopectin

The amount of swollen or dissolved amylose and amylopectin is determined by dispersing about 1 g of dried starch powder in 100 cm^3 of pure water, allowing the resulting dispersion to stand for 16 hours, calculating the volume of the upper layer portion of the dispersion separated into upper and lower layers and the weight percentage of solids in 30 cm^3 of the upper layer, and calculating the amount by the following equation:

The amount (%) of swollen or dissolved amylose and amylopectin = the volume (cm^3) of the upper layer portion ÷ 30 x the weight of solids in 30 cm^3 of the upper layer ÷ the dry weight of the starch powder x 100 (%)

[0043]

(5) Degree of swelling (cm^3/g)

Degree of swelling is determined by dispersing about 1 g of dried starch powder in 100 cm^3 of pure water, allowing the resulting dispersion to stand for 16 hours, and calculating the degree of swelling from the volume V of the lower layer portion of the dispersion separated into upper and lower layers, by the following equation:

Degree of swelling (cm^3/g) = V / the dry weight of the starch powder

(6) Shell thin-film structure

One gram of starch powder is dispersed in 100 cm^3 of pure water and after standing for 16 hours, the lower layer portion of the dispersion separated into upper and lower layers is observed under an optical microscope (magnification: 10). In the case of the starch powder of the invention, the shell thin-film structure inherent in a starch raw material for the starch powder is completely present without loss thereof. On the other hand, in the case of pregelatinized starch, nothing is observed, or a flaky, massive or the like shell structure formed by the

conversion of swollen or dissolved amylose and amylopectin to β-amylose and β-amylopectin is observed.

[Example 1]

[0044]

Potato starch was packed in a stainless-steel vat (50 cm x 25 cm) to a thickness of 5 cm, subjected to pressure reduction (600 mmHg) in a pressure container for 5 minutes, and then treated with compressed steam (120°C) for 20 minutes. Using the treated potato starch as a starting material, a starch emulsion having a solid concentration of 5% was prepared. The starch emulsion was gelatinized by heating at 95°C for 45 minutes in a jacketed agitation vessel (4 L), diluted 2-fold with warm water at 60°C, and then continuously spray-dried at a flow rate of 8.3 L/hr while being maintained at 60°C, to obtain starch powder A. A cylindrical molded article with a diameter of 0.8 cm was obtained by compressing 0.2 g of prepared powder of acetaminophen (APAP)/starch powder A/crystalline cellulose "Ceolus" KG-802 (10/60/30) at 60 MPa with a static-pressure press, and was subjected to a release-by-dissolution test. As test solutions, solution I (pH 1.2), solution II (pH 6.8, ionic strength 0.14) and Mcilvaine solution (pH 7.2, ionic strength 0.39) were used as described in the Japanese Pharmacopoeia. The test was carried out by adding α-amylase to each of these solutions to a concentration of 5 $\mu m/cm^3$.

[0045]

Table 1 shows the physical properties of starch powder, and Table 2 shows the release-by-dissolution test result of the molded article of the prepared powder. Table 3 shows the result of subjecting the cylindrical molded article to a release-by-dissolution test in the same manner as above after storing the cylindrical molded article in a sealed-in state at 40°C and 75%RH for 2 weeks.

The molded article containing starch powder A had a sustained-release capability equal to that imparted by release-sustaining base ingredients that have been generally used. In addition, the molded article was free from pH dependence and the influence of ionic strength and moreover, had a good stability over a long period of time. Thus, it can be seen that the molded article is an excellent pharmaceutical preparation.

[Example 2]

[0046]

Potato starch was packed in a stainless-steel vat (50 cm x 25 cm) to a thickness of 5 cm, subjected to pressure reduction (600 mmHg) in a pressure container for 5 minutes, and then treated with compressed steam (120°C) for 20 minutes. Using the treated potato starch as a starting material, a starch emulsion having a solid concentration of 5% was prepared. The starch emulsion was gelatinized (outlet temperature: 105°C) by heating at 20 L/hr in a jet cooker, continuously passed through a

residence tube (85°C) with a capacity of 3 L, and then spray-dried to obtain starch powder B. The residence time was 9 minutes.

A release-by-dissolution test on a molded article of prepared powder was carried out by the same procedure as in Example 1 except for using starch powder B in place of starch powder A. Table 1 shows the physical properties of starch powder and Table 2 shows the release-by-dissolution test result of the molded article of prepared powder.

The molded article containing starch powder B had a sustained-release capability equal to that imparted by release-sustaining base ingredients that have been generally used. In addition, the molded article was free from pH dependence and the influence of ionic strength. Thus, it can be seen that the molded article is an excellent pharmaceutical preparation.

[Example 3]

[0047]

Potato starch was packed in a stainless-steel vat (50 cm x 25 cm) to a thickness of 5 cm, subjected to pressure reduction (600 mmHg) in a pressure container for 5 minutes, and then treated with compressed steam (120°C) for 20 minutes. Using the treated potato starch as a starting material, a starch emulsion having a solid concentration of 5% was prepared. The starch emulsion was gelatinized (outlet temperature: 120°C) by heating at 20 L/hr in a jet cooker, continuously passed through a

residence tube (120°C) with a capacity of 3 L, and then spray-dried to obtain starch powder C. The residence time was 9 minutes.

A release-by-dissolution test on a molded article of prepared powder was carried out by the same procedure as in Example 1 except for using starch powder C in place of starch powder A. Table 1 shows the physical properties of starch powder, and Table 2 shows the release-by-dissolution test result of the molded article of prepared powder.

The molded article containing starch powder C had a sustained-release capability equal to that imparted by release-sustaining base ingredients that have been generally used. In addition, the molded article was free from pH dependence and the influence of ionic strength. Thus, it can be seen that the molded article is an excellent pharmaceutical preparation.

[0048]

Comparative Example 1

A release-by-dissolution test on a molded article of prepared powder was carried out by the same procedure as in Example 1 except for using commercial potato pregelatinized starch (Matsunorin M, mfd. by Matsutani Chemical Industry Co., Ltd.) in place of starch powder A. Table 1 shows the physical properties of the commercial potato pregelatinized starch, and Table 2 shows the release-by-dissolution test result of the molded article of prepared powder.

The commercial potato pregelatinized starch had a collapse time of 3 hr or more, but it could not have a sufficient release-sustaining capability because of its low water retention capacity and low gel indentation load and it exhibited no release-sustaining capability at a high pH or a high ionic strength.

[0049]

Comparative Example 2

A release-by-dissolution test on a molded article of prepared powder was carried out by the same procedure as in Example 1 except for using commercial corn pregelatinized starch (mfd. by Sanwa Cornstarch Co., Ltd.) in place of starch powder A. Table 1 shows the physical properties of the commercial corn pregelatinized starch, and Table 2 shows the release-by-dissolution test result of the molded article of prepared powder.

The commercial corn pregelatinized starch had a collapse time of 3 hr or more and a sufficient water retention capacity but it had substantially no release-sustaining capability because of its low gel indentation load.

[0050]

Comparative Example 3

A release-by-dissolution test on a molded article of prepared powder was carried out by the same procedure as in Example 1 except for using commercial high-amylose corn pregelatinized starch (mfd. by Sanwa

Cornstarch Co., Ltd.) in place of starch powder A. Table 1 shows the physical properties of the commercial high-amylose corn pregelatinized starch, and Table 2 shows the release-by-dissolution test result of the molded article of prepared powder.

The commercial high-amylose corn pregelatinized starch had a collapse time of 3 hr or less and an insufficient water retention capacity and exhibited no release-sustaining properties at all.

[0051]

Comparative Example 4

A release-by-dissolution test on a molded article of prepared powder was carried out by the same procedure as in Example 1 except for using commercial waxy corn pregelatinized starch (mfd. by Sanwa Cornstarch Co., Ltd.) in place of starch powder A. Table 1 shows the physical properties of the commercial waxy corn pregelatinized starch, and Table 2 shows the release-by-dissolution test result of the molded article of prepared powder.

The commercial waxy corn pregelatinized starch had a sufficient water retention capacity but it had a collapse time of 3 hr or less and exhibited no release-sustaining properties at all.

[0052]

Comparative Example 5

A release-by-dissolution test on a molded article of prepared powder was carried out by the same

procedure as in Example 1 except for using commercial partly pregelatinized starch (PCS, mfd. by Sanwa Cornstarch Co., Ltd.) in place of starch powder A. Table 1 shows the physical properties of PCS, and Table 2 shows the release-by-dissolution test result of the molded article of prepared powder.

PCS had an insufficient water retention capacity and a collapse time of 3 hr or less and exhibited no release-sustaining properties at all.

[0053]

Comparative Example 6

A release-by-dissolution test on a molded article of prepared powder was carried out by the same procedure as in Example 1 except for using commercial partly pregelatinized starch (Starch 1500) in place of starch powder A. Table 1 shows the physical properties of Starch 1500 and Table 2 shows the release-by-dissolution test result of the molded article of prepared powder.

Starch 1500 had an insufficient water retention capacity and a collapse time of 3 hr or less and exhibited no release-sustaining properties at all.

[0054]

Comparative Example 7

A release-by-dissolution test on a molded article of prepared powder was carried out by the same procedure as in Example 1 except for using a commercial release-sustaining base ingredient of non-starch type

(HPMC 60SH, mfd. by Shin-Etsu Chemical Co., Ltd.) in place of starch powder A. Table 1 shows the physical properties of HPMC 60SH and Table 2 shows the release-by-dissolution test result of the molded article of prepared powder.

HPMC 60SH was sufficient in collapse time, gel indentation load and release-sustaining capability and desirably had no pH dependence. But HPMC 60SH had an insufficient water retention capacity and it can be seen that at a high ionic strength, HPMC 60SH becomes unable to be sufficiently hydrated, and exhibited no release-sustaining properties at all.

[0055]

[Table 1]

Sample	Water retention capacity (%)	Collapse time (hr)	Gel indentation load (g)	Amount of swollen or dissolved amylose and amylopectin (%)	Degree of swelling (cm^3/g)	Shell thin-film structure
Example 1	1435	≧3	1100	43	33	Yes
Example 2	1383	≧3	700	48	29	Yes
Example 3	738	≧3	≧2000	72	5	Yes
Comparative Example 1	606	≧3	200	91	2	No
Comparative Example 2	1284	≧3	75	19	19	No (flaky)
Comparative Example 3	364	0.8	Not measurable	22	5	No (massive)
Comparative Example 4	1046	2.8	Not measurable	57	15.5	No
Comparative Example 5	511	0.5	Not measurable	2	8.6	Yes
Comparative Example 6	356	0.3	Not measurable	11	9	Yes
Comparative Example 7	682	≧3	≧2000	-	-	-

[0056]

[Table 2]

	APAP release-by-dissolution rate after 2 hr (%)			APAP release-by-dissolution rate after 5 h (%)		
Sample	Solution I•α-amylase	Solution II•α-amylase	Mcilvaine•α-amylase	Solution I•α-amylase	Solution II•α-amylase	Mcilvaine•α-amylase
Example 1	39	39	33	66	70	62
Example 2	38	38	32	65	73	65
Example 3	38	46	43	61	71	65
Comparative Example 1	35	64	100	60	94	100
Comparative Example 2	81	81	100	90	100	100
Comparative Example 3	100	100	100	100	100	100
Comparative Example 4	100	100	100	100	100	100
Comparative Example 5	100	100	100	100	100	100
Comparative Example 6	100	100	100	100	100	100
Comparative Example 7	39	41	100	73	70	100

[0057]

[Table 3]

	APAP release-by-dissolution rate at the beginning (%)		APAP release-by-dissolution rate after standing for 2 weeks (%)	
Sample	Solution II•α-amylase 2 hr after	Solution II•α-amylase 5 hr after	Solution II•α-amylase 2 hr after	Solution II•α-amylase 5 hr after
Example 1	39	70	42	70

[Kind of Document] Abstract

[Abstract]

[Problem]

To provide a novel starch-based release-sustaining base ingredient which is as follows: the base ingredient is starch powder as a release-sustaining base ingredient for controlling the concentration of an active ingredient(s); it is a release-sustaining base ingredient which has a sufficient release-sustaining capability to constitute a sustained-release preparation mainly for medicinal use, assures pH stability and long-term stability, and is convenient; and since it is not affected by inoic strength, it is free from the dose dumping problem, so that it permits accurate control of an active ingredient(s)

[Solution]

A composition comprising starch powder having a water retention capacity of 700% or more, a collapse time of 3 hr or more and a gel indentation load of 400 g or more, and one or more active ingredients.

[Selected Drawing] None.